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(54) Title: PHARMACEUTICAL AND/OR COSMETICAL COMPOSITIONS

(57) Abstract: The present invention relates to the use of pantothenic acid and/or its derivatives for treating dermatological disorders which involve the degranulation process of the mastocytes, such as atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus. The present invention also relates to pharmaceutical and/or cosmetic compositions comprising pantothenic acid and/or its derivatives, glycine and pharmaceutically and/or cosmetically acceptable additives. The inhibition effect on the degranulation process of the mastocytes is strongly increased if the pantothenic acid and/or its derivatives are combined with glycine. A synergic effect in the inhibition by the mixture in comparison with the single compounds is therefore observed.

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Pharmaceutical and/or cosmetical compositions

The present invention relates to pharmaceutical and/or cosmetical compositions and, more precisely, to compositions for blocking the histamine release by the mastocytes.

The degranulation of the cutaneous mastocytes leads to the release of several mediators,  
5 like for instance the histamine which is responsible for the occurrence of different reactions such as pruritus. The histamine release can be modulated by several substances which can either amplify or inhibit it, wherein the inhibitors can be used as active compounds in medicaments.

For a few types of pruritus, like the allergic pruritus, the stimulus responsible for the  
10 degranulation of the mastocytes is due to a modification of the mastocyte membrane structure by a bipolar antigen fixed on two IgE which, on their turn, are unspecifically attached to the cell membrane by their Fc extremities.

For many kinds of pruritus, the mechanisms are however still obscure. The stimuli may be in fact of different nature, both chemical and physical, and may involve the presence of a  
15 neurotransmitter such as the substance P. This substance, present naturally in the mammal body, is capable of initiating the degranulation process of the mastocytes. A pruritus can be therefore treated in different ways, e.g. by blocking the message transmission from the central nervous system, by blocking the stimulus and/or by inhibiting the degranulation process.

20 Pantothenic acid, which is also known as D(+) N-(2,4-dihydroxy-3,3-dimethylbutyryl) $\beta$ -alanine, is a member of the B complex vitamins and is sometimes referred to as vitamin B<sub>5</sub>.

Pantothenic acid plays a key role in cellular metabolism, as after incorporation into coenzyme A (CoA), it participates in the synthesis of fatty acids, cholesterol and sterols. Through its participation in the Krebs cycle, coenzyme CoA is also instrumental in the  
25 generation of energy by the cells. Pantothenic acid is hence essential for epithelial regeneration and development in the event of damage to the skin when a high rate of lipids and cellular renewal is needed.

Dexpanthenol, the alcohol of the pantothenic acid, is well absorbed by the skin. After penetration in the skin it is rapidly transformed into pantothenic acid. Dexpanthenol has therefore been used for many years in topical products such as ointments and creams. The clinical effectiveness of the topical application of dexpanthenol in promoting wound  
5 healing has been confirmed by several studies in cases of wounds, burns, cracked nipples, ulcers, and bedsores (e.g. P.Girard, A.Béraud, C.Goujon, A.Sirvent, J-L Foyatier, B. Alleaume, R. de Bony, *Les Nouvelles Dermatologiques*, 17, 1998, pp. 559-570).

It has been now surprisingly found that compositions containing pantothenic acid and/or its derivatives can be used for treating pruriginous conditions. It has been observed that  
10 pantothenic acid and/or its derivatives inhibit the degranulation process of the mastocytes, thus diminishing the amount of mediators released into the extra-cellular environment. Pantothenic acid and/or its derivatives can be therefore used for all dermatological disorders which involve the degranulation process of the mastocytes, such as atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites,  
15 skin allergies, senile pruritus, etc.

In a preferred embodiment of the present invention, the pantothenic acid and/or its derivatives are used in a pharmaceutical and/or cosmetical composition in an amount varying between 0,1 and 10% of its total weight and, preferably, in an amount varying between 2 and 5% of the total weight of the pharmaceutical and/or cosmetical  
20 composition.

Any pharmaceutically and/or cosmetically acceptable derivative of pantothenic acid can be used in the compositions of the present invention. Examples include alcohols, aldehydes, alcohol esters, acid esters and the like. The preferred derivative of pantothenic acid is pantothenyl alcohol (panthenol), particularly the D(+) of pantothenyl alcohol which is  
25 more commonly known as dexpanthenol. As preferred alcohol ester, pantothenyl triacetate can be chosen.

The present invention relates also to the use of pantothenic acid and/or its derivatives for the manufacture of topically applicable pharmaceutical and/or cosmetical compositions for treating dermatological disorders which involve the degranulation process of the  
30 mastocytes, such as atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus, etc.

Preferably, the pantothenic acid and/or its derivatives are present in an amount varying between 0,1 and 10% of the total weight of the pharmaceutical and/or cosmetical composition and, more preferably, in an amount varying between 2 and 5% of the total  
35 weight of the pharmaceutical and/or cosmetical composition.

Another aspect of the present invention relates to pharmaceutical and/or cosmetic compositions comprising pantothenic acid and/or its derivatives, glycine and pharmaceutically and/or cosmetically acceptable additives.

5 Glycine is an amino-acid naturally occurring in most animal species. It inhibits the histamine release by mastocytes. The effect of the glycine on the mastocyte degranulation is described, for instance, in M. Paubert-Braquet, G. Lefrançois, S. Picquot, D. Rod, *Thérapeutique*, 95, 1992, 2. An inhibition effect on the degranulation process of the mastocytes has been observed, wherein a decrease in the amount of mediators released into the extra-cellular environment (e.g. histamine) is observed.

10 The use of the glycine for treating dermatological disorders which involve the degranulation process of the mastocytes is furthermore described in A. Siboulet, JM Bohbot, *Gyn. Obs.*, 1987, 166 by means of a study on pruriti in the genital area.

It has been now surprisingly found that the inhibition effect on the degranulation process of the mastocytes is strongly increased if the pantothenic acid and/or its derivatives are  
15 combined with glycine. A synergic effect in the inhibition by the mixture in comparison with the single compounds is therefore observed.

The synergic effect obtained by mixing the above compounds together lead to several important advantages. For the same effect, it is possible to reduce the concentrations of the active compounds, thus decreasing the risk of intolerance for the patients.

20 A lower concentration of the active compounds lead also to lower manufacture costs and, therefore, to lower selling prices of the compositions. With the same therapeutic effect, the compositions according to the present invention are therefore more tolerable and more competitive than the conventional ones.

According to a preferred embodiment of the present invention, the ratio between the  
25 pantothenic acid and/or its derivatives and the glycine varies between 0.13 and 13.3 wt/wt.

A further aspect of the present invention is related to the use of a mixture of pantothenic acid and/or its derivatives and glycine for the manufacture of a medicament for treating dermatological disorders which involve the degranulation process of the mastocytes, such as atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to  
30 insect bites, skin allergies, senile pruritus, etc.

Preferably, the pantothenic acid and/or its derivatives and the glycine are present in the mixture in a ratio varying between 0.13 and 13.3 wt/wt.

Pantothenic acid and/or its derivatives and the mixtures of pantothenic acid and/or its derivatives and glycine can be administered orally or be applied topically to the skin of a mammal at the site of the disorder.

5 Pantothenic acid and/or its derivatives and the mixtures of pantothenic acid and/or its derivatives and glycine can be administered orally in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The active compounds can be processed with pharmaceutically inert, inorganic or organic excipients, such as lactose, corn starch or derivatives thereof, talc, stearic acid or its salts. Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid  
10 polyols etc. Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Moreover, the pharmaceutical and/or cosmetical compositions can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also  
15 contain still other therapeutically valuable substances, such as further vitamins, minerals, sun filters, phytotherapeutic extracts, etc.

For topical administration, the above active compounds are conveniently used in the form of pharmaceutical and/or cosmetical preparations or compositions which further contain an acceptable carrier material. Topical dosage forms provided by the invention generally  
20 contain 0.1 to 10 weight percent of active compound, based on the total weight of the dosage form. However, higher or lower concentrations can also be present depending on the dosage form which is used. The topical preparations of the present invention can be applied in an amount and under a time schedule varying with the needs of the patient.

The term "topical" as used in the present specification relates to the use of the above active  
25 compounds, which are processed with a suitable carrier material and which is applied to the skin or mucous membrane, so that it can display local activity. Accordingly, the topical forms embrace pharmaceutical and/or cosmetical dosage forms which are suitable for external use, so that a direct contact with the skin results. The topical dosage forms embrace gels, creams, lotions, salves, powders, aerosols and other conventional forms  
30 which are suitable for the direct application of products on the skin or mucous membrane. These dosage forms can be manufactured by mixing the above compounds with known carrier materials which are suitable for topical use.

Salves and creams contain oily, absorbent, water-soluble and/or emulsifying carrier materials such as vaseline, paraffin oil, propylene glycol, cetylalcohol, glycerine  
35 monostearate, alkyl-branched fatty acids and the like.

Lotions are liquid preparations and can vary from simple solutions to aqueous or aqueous/alcoholic preparations which contain the substances in finely divided form. The preparations contain suspended or dispersing substances such as, for example, sodium carboxymethylcellulose which suspend or disperse the active substance in a carrier  
5 prepared from water, alcohol, glycerine and the like.

Gels are semi-solid preparations which are obtained by gelling a solution or suspension of the active substance in a carrier material. The carrier materials, which can be hydrophilic or hydrophobic, are gelled using a gelling agent in form of polymers of biological, natural or synthetical origin.

10 Aerosols are solutions or suspensions of the active substance in a carrier material which are applied using spray generators. Usually used carriers are, for example, trichloromonofluoromethane, trichlorodifluoromethane, volatile silicones, nitrogen, etc..

Spays are solutions suspensions or powders of the active substance in a carrier material which are applied using mechanical pums.

15 The compositions according to the present invention are used by applying an amount of the active compounds sufficient to provide a therapeutic and/or cosmetic effect to the skin to be treated. This application can be effected in the usual manner by rubbing, spraying or by a plaster.

The topical compositions are usually applied in an amount to provide from 0.1 to 5 mg of  
20 active ingredient per cm<sup>2</sup> of the skin per day.

It is also an object of the present invention to provide a process for preparing the above pharmaceutical and/or cosmetical compositions, comprising mixing pantothenic acid and/or its derivatives with glycine.

The following examples further illustrate the invention. Glycine and calcium pantothenate  
25 were provided by ROCHE and they were conserved at 4°C until their use. Substance P was provided by SIGMA and the analytic reagents were provided by SIGMA, MERCK, BDH, ALDRICH, FLUKA or CARLO ERBA unless otherwise specified.

Tests were carried out on peritoneal mastocytes of rat stimulated by the substance P (10µM), or on human skin tissue.

30 Peritoneal mastocytes of rat

Peritoneal mastocytes of rat were incubated with the test products and the substance P for 2 minutes at 37°C in the following medium: sodium phosphate buffer 4 mM; potassium

phosphate buffer 2.7 mM; NaCl 0.145 M; KCl 2.7 mM; CaCl<sub>2</sub> 0.9 mM; BSA (bovine serum albumin) 0.175% (w/v). At the end of the incubation, histamine released by the mastocytes was quantified by spectrofluorimetry with ortho-phthalaldehyde (OPT) (R. Hakanson, A.I. Ronnberg and K. Sjolund, *Analy. Biochem.*, 47, 1972, pp. 356-370). The measurements were carried out by means of a multiplate spectrofluorimeter (Cytofluor 2350, MILLIPORE). Data groups (control and treated groups) were compared using a one-way analysis of variance (ANOVA 1,  $p < 0.05$ ), following by a Dunnett' test ( $p < 0.05$ ).

Glycine and calcium pantothenate were tested in combination as follow:

Table 1: Test combinations.

| Ca-pantothenate<br>( $\mu\text{g/ml}$ ) | Glycine ( $\mu\text{g/ml}$ ) |       |       |       |       |
|---|------------------------------|-------|-------|-------|-------|
| 10                                      | 7.50                         | 18.75 | 37.50 | 56.25 | 75.00 |
| 25                                      | 7.50                         | 18.75 | 37.50 | 56.25 | 75.00 |
| 50                                      | 7.50                         | 18.75 | 37.50 | 56.25 | 75.00 |
| 75                                      | 7.50                         | 18.75 | 37.50 | 56.25 | 75.00 |
| 100                                     | 7.50                         | 18.75 | 37.50 | 56.25 | 75.00 |

10

The inhibition of the histamine release for different compositions tested on peritoneal mastocytes of rat is depicted in Table 2.

Table 2: Inhibition in Peritoneal mastocytes of rat.

| Example | Ca-pantothenate<br>( $\mu\text{g/ml}$ ) | Glycine ( $\mu\text{g/ml}$ ) | Inhibition <sup>(1)</sup> |
|---------|---|------------------------------|---------------------------|
| 1       | 0                                       | 0                            | 100                       |
| 2       | 10                                      | 0                            | 100                       |
| 3       | 0                                       | 7.5                          | 100                       |
| 4       | 10                                      | 7.5                          | 48                        |

|    |     |       |     |
|----|-----|-------|-----|
| 5  | 10  | 18.75 | 44  |
| 6  | 10  | 37.50 | 1   |
| 7  | 10  | 56.25 | 21  |
| 8  | 10  | 75.00 | -11 |
| 9  | 25  | 7.5   | 65  |
| 10 | 25  | 18.75 | 49  |
| 11 | 25  | 37.50 | -14 |
| 12 | 25  | 75.00 | -8  |
| 13 | 50  | 7.5   | 54  |
| 14 | 50  | 18.75 | 48  |
| 15 | 50  | 37.50 | 31  |
| 16 | 50  | 56.25 | 13  |
| 17 | 50  | 75.00 | 9   |
| 18 | 75  | 7.5   | 63  |
| 19 | 75  | 18.75 | 49  |
| 20 | 75  | 37.50 | 35  |
| 21 | 75  | 75.00 | 14  |
| 22 | 100 | 7.5   | 59  |
| 23 | 100 | 18.75 | 41  |
| 24 | 100 | 37.50 | 29  |
| 25 | 100 | 56.25 | 10  |
| 26 | 100 | 75.00 | 12  |



- <sup>(1)</sup> amount of histamine released by the mastocytes. Value 100 refers to the amount of histamine released by the substance P in absence of Ca-pantothenate and/or glycine, while value 0 refers to the release of histamine in normal conditions, i.e. in the absence of histamine release inducing agents. Negative values represent histamine concentrations which are lower than those observable at normal conditions.

The data in table 2 show that mixtures of Ca-panthothenate and glycine in different concentrations strongly inhibit the histamine release.

- It has been furthermore shown that a synergic effect resulting from combining Ca-panthothenate and glycine occurs. Concentrations of 10 µg/ml of Ca-panthothenate and 7.5 µg/ml of glycine, if taken separately, do not act as inhibitors while, if taken together, they strongly block the histamine release (see examples 2, 3 and 4 in table 2). This synergic effect enables to strongly decrease the concentrations of the active compounds in the medicaments, thus improving their tolerance and decreasing their manufacture costs.

#### Human skin tissue

- The skin tissue assay system was prepared from normal adult skin collected after an abdominal plastic surgery. The subject was a 68 years old woman (subject M1085). The skin tissue specimen was rinsed in Krebs bicarbonate solution consisting of: NaCl 118 mM; KCl 5.4 mM; NaH<sub>2</sub>PO<sub>4</sub> 1 mM; MgSO<sub>4</sub> 1.2 mM, CaCl<sub>2</sub> 1.9 mM; NaHCO<sub>3</sub> 25 mM and D-glucose 11.1 mM. Skin discs of about 8 mm of diameter were performed. Skin discs were cultured in RPMI 1640 medium supplemented with penicillin (100 UI/ml), streptomycin (110 µg/ml) and 2 mM glutamine. Skin discs were maintained at 37°C in a humidified incubator under a 5% CO<sub>2</sub>/95% air atmosphere. Test products were incubated with the human skin discs and 100 µM of substance P for 2 hours at 37°C.

- At the end of the incubation, histamine released by the human skin discs was quantified by ELISA (IMMUNOTECH). The results were expressed as pmoles of histamine released per gram of skin. Data groups (control and treated groups) were compared using a one-way analysis of variance (ANOVA 1, p<0.05), following by a Dunnett's test (p<0.05).

The inhibition of the histamine release for different compositions tested on human skin is depicted in Table 3.

| Ca-pantothenate<br>(µg/ml) | Glycine (µg/ml) | Inhibition <sup>(1)</sup> |
|----------------------------|-----------------|---------------------------|
| 25                         | 0               | 84                        |

|     |    |    |
|-----|----|----|
| 50  | 0  | 84 |
| 100 | 0  | 80 |
| 100 | 75 | 60 |

- <sup>(1)</sup> amount of histamine released by the mastocytes. Value 100 refers to the amount of histamine released by the substance P in absence of Ca-pantothenate and/or glycine, while value 0 refers to the release of histamine in normal conditions, i.e. in the absence of histamine release inducing agents. Negative values represent histamine concentrations which are lower than those observable at normal conditions.

The data of table 3 show that Ca-pantothenate acts as inhibitor of the histamine release already at a concentration of 25 µg/ml and that the addition of glycine further improves such inhibition.

#### Example 1

- 10 Ointment containing dexpanthenol and glycine.

The topical composition is prepared by combining the following components utilizing conventional techniques:

|    |                 |         |
|----|-----------------|---------|
|    | Dexpanthenol    | 5 wt%   |
|    | Glycine         | 3 wt%   |
| 15 | Cetyl alcohol   | 1.5 wt% |
|    | Stearyl alcohol | 1.5 wt% |
|    | Lanolin alcohol | 1.5 wt% |
|    | Glyceryl oleate | 1.5 wt% |
|    | Almond oil      | 4.0 wt% |
| 20 | White wax       | 5.5 wt% |
|    | Wool fat        | 25 wt%  |
|    | Vaseline white  | 10 wt%  |
|    | Paraffin liquid | 15 wt%  |
|    | Ozokerite       | 1.5 wt% |
| 25 | Water           | balance |

#### Example 2

Lotion containing dexpanthenol and glycine.

The topical composition is prepared by combining the following components utilizing conventional techniques:

|    |                 |         |
|----|-----------------|---------|
|    | Dexpanthenol    | 2 wt%   |
|    | Glycine         | 0.2 wt% |
| 5  | PEG-6-stearat   | 4 wt%   |
|    | Dimethicone     | 1.5 wt% |
|    | Paraffin liquid | 4 wt%   |
|    | Pantolactone    | 0.2wt%  |
|    | EDTA            | 0.2wt%  |
| 10 | Phenoxyethanol  | 0.7wt%  |
|    | Perfume         | 0.5 wt% |
|    | Water           | balance |

### Example 3

- 15 Capsules containing dexpanthenol and glycine

The oral composition is prepared by combining the following components utilizing conventional mixing techniques:

|    |                     |                |
|----|---------------------|----------------|
|    | Dexpanthenol        | 100 mg/capsule |
|    | Glycine             | 50 mg/capsule  |
| 20 | Polyethylen glycol  | 1.5 mg/capsule |
|    | Starch              | 50 mg/capsule  |
|    | Magnesium stearate, | 1.5 mg/capsule |
|    | Lactose             | 100 mg/capsule |
|    | Talc                | 1.5 mg/capsule |

Claims

1. Use of pantothenic acid and/or its derivatives for treating dermatological disorders which involve the degranulation process of the mastocytes.
2. The use according to claim 1 for treating atopic dermatitis, psoriasis, contact eczema,  
5 skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus.
3. The use according to claim 1 or 2, wherein the pantothenic acid and/or its derivatives are included in a pharmaceutical and/or cosmetical composition in an amount varying between 0.1 and 10% of its total weight.
4. The use according to claim 3, wherein the pantothenic acid and/or its derivatives are  
10 present in an amount varying between 2 and 5% of the total weight of the pharmaceutical and/or cosmetical composition.
5. Use of pantothenic acid and/or its derivatives for the manufacture of orally or topically administerable pharmaceutical and/or cosmetical compositions for treating dermatological disorders which involve the degranulation process of the mastocytes.
- 15 6. The use according to claim 5 for treating atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus.
7. The use according to claim 5 or 6, wherein the pantothenic acid and/or its derivatives are present in an amount varying between 0.1 and 10% of the total weight of the pharmaceutical and/or cosmetical composition.
- 20 8. The use according to claim 7, wherein the pantothenic acid and/or its derivatives are present in an amount varying between 2 and 5% of the total weight of the pharmaceutical and/or cosmetical composition.
9. Pharmaceutical and/or cosmetical composition comprising pantothenic acid and/or its derivatives, glycine and pharmaceutically and/or cosmetically acceptable additives.
- 25 10. The pharmaceutical and/or cosmetical composition of claim 9, wherein the ratio between the pantothenic acid and/or its derivatives and the glycine varies between 0.13 and 13.3 wt/wt.
11. The pharmaceutical and/or cosmetical composition of claim 9 or 10, wherein the  
30 pantothenic acid and/or its derivatives and glycine are present each in an amount varying between 0.1 and 10% of the total weight of the pharmaceutical and/or cosmetical composition.

12. The pharmaceutical and/or cosmetical composition of claim 11, wherein the pantothenic acid and/or its derivatives and glycine are present each in an amount varying between 2 and 5% of the total weight of the pharmaceutical and/or cosmetical composition.
- 5 13. Use of a mixture of pantothenic acid and glycine for treating dermatological disorders which involve the degranulation process of the mastocytes.
14. The use of claim 11 for treating atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus.
- 10 15. The use of claim 13 or 14, wherein the ratio between the pantothenic acid and/or its derivatives and the glycine varies between 0.13 and 13.3 wt/wt.
16. Use of a mixture of pantothenic acid and glycine for the manufacture of a medicament and/or a cosmetical composition for treating dermatological disorders which involve the degranulation process of the mastocytes.
- 15 17. The use of claim 16 for treating atopic dermatitis, psoriasis, contact eczema, skin allergies, skin inflammation due to insect bites, skin allergies, senile pruritus.
18. The use according to claim 16 or 17, wherein the pantothenic acid and the glycine are present in the mixture in a ratio varying between 0.13 and 13.3 wt/wt.
19. Process for preparing a pharmaceutical and/or cosmetical composition according to any one of claims 9 to 12, comprising mixing pantothenic acid and/or its derivatives with glycine.
- 20 20. The invention substantially as described herein.

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# INTERNATIONAL SEARCH REPORT

International Application No

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A          | DE 195 37 509 A (EGSTO PHARM<br>PHARMAZEUTISCHE PR)<br>10 April 1997 (1997-04-10)  |                       |
| A          | WO 93 21899 A (PROCTER & GAMBLE)<br>11 November 1993 (1993-11-11)                  |                       |
| A          | US 5 304 574 A (LEUNG LIT-HUNG)<br>19 April 1994 (1994-04-19)                      |                       |
| A          | US 4 721 705 A (SCHREUDER JOHANNES C P)<br>26 January 1988 (1988-01-26)            |                       |
| A          | DE 198 00 982 A (FOERSTER KARL HEINZ)<br>15 July 1999 (1999-07-15)                 |                       |
| A          | US 5 827 523 A (HOLLAND DENNIS A)<br>27 October 1998 (1998-10-27)                  |                       |
|            | -/--   |                       |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
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